

Description**BACKGROUND OF THE INVENTION**

5 The frequency of infection associated with the use of invasive medical devices such as insertable as well as implantable devices is well documented. In the case of insertable devices such as catheters, the rate of infection necessitates frequent replacement. In the case of implantable devices such as prosthetic devices, infections interfere with adaptation to the device. In either case, life-threatening septicemia can result from such infections.

10 The pathophysiology of medical device related infections is complex. Many factors influence the risk and type of infection. These include factors related to the host, to the medical device and to the virulence and inoculum of the infecting organism. Hundreds of medical publications have investigated and documented the variables that contribute to these factors. It has been well established that the overwhelming majority of medical device associated infections occur when bacteria colonize and then migrate along the medical device until they gain access to the bloodstream. Accordingly, the ability of bacteria to adhere to a medical device is important to the successful establishment of an infection.

15 The role of bacterial surface polysaccharides in adherence is well established. Over 12 years ago a series of experiments demonstrated the ubiquitous nature of these polysaccharides. Surface polysaccharides are found on most bacteria and fungi. When confronted with a specific lectin, the surface polysaccharides generate a glycocalyx that surrounds the bacteria and adhering surface. The glycocalyx consists of a mass of long polysaccharide fibers and appears to have several functions. It may act as a source of nutrition for the bacteria. It may serve as a physical barrier.

20 Most importantly, surface polysaccharides determine the specific surface interactions of the bacterial cell.

This phenomena has far reaching effects. For example the ability of *Streptococcus mutans* to colonize teeth, *Streptococcus salivarius* to colonize gums, *Bacteroides fragilis* to colonize the intestine, and Group A streptococci to colonize the throat and skin are all manifestations of a complex interaction between specific surface polysaccharides and specific lectins, which are proteins that bind to specific polysaccharides.

25 The importance of bacterial surface and medical device related infections is best illustrated by coagulase negative staphylococci. *S. epidermidis*, the most important and common of the coagulase negative staphylococci, was previously considered a non-pathogenic organism. It has now emerged as the most common cause of foreign body infection and nosocomial sepsis. It is the major cause of prosthetic valve endocarditis, vascular graft infection, artificial hip and knee infection, and catheter related sepsis. Although less virulent than *S. aureus* and many other bacteria, it is highly resistant to most antimicrobials except vancomycin and rifampin.

In the early 1980's, electron microscopy studies demonstrated that certain strains of *S. epidermidis* produce an extracellular slime like substance. The extracellular slime is a complex substance composed mostly of polysaccharide.

The production of a surface polysaccharide biofilm or slime by an organism enables it to adhere to surfaces of insertable or implantable devices and cause infection. The slime appears to contain a galactose rich polysaccharide "adhesive" which mediates attachment of the organism to polymers. It also contains a polysaccharide substance that accumulates after adherence occurs and cements the organism to the medical device.

35 Besides adhesion, the slime appears to have other functions. It binds to glycopeptide antibiotics including vancomycin. This may explain why most *S. epidermidis* infections do not respond to antimicrobial therapy alone. When infection occurs on an inserted or implanted device, removal of the device is usually required. Slime also interferes with certain immune responses.

40 The extracellular slime of *S. epidermidis* is really a manifestation of exuberant production of surface polysaccharide. The quantitative production appears to be regulated by a complex mechanism that turns on and off production based upon the local environment. Although *S. epidermidis* has been the focus of much of the research on foreign-body infections, this concept has been studied in other organisms. Colonization by *Pseudomonas* species on the interior surface of PVC and other pipes has demonstrated a glycocalyx mass that shields organisms from disinfectants including chlorine, phenolics, quaternary ammonium, and iodophor disinfectants. Once a bacterial glycocalyx is formed, it is very difficult to break down.

45 The development of polymers that contain antimicrobial properties has important implications for both medicine and industry. Aside from factors related to bacterial polysaccharides, the coating of the foreign body by proteins (albumin, fibronectin, platelets) from the host, as well as a variety of factors related to the polymer itself undoubtedly affect the risk of infection.

50 Several approaches have been utilized to produce medical devices made of or with polymers with antimicrobial properties, as described, for example, in U.S. 4,769,013, U.S. 4,713,402 and U.S. 4,886,505. Antimicrobial agents can be incorporated during the production process or grafted into the surface as described in U.S. 4,925,668. However, even broadspectrum antibiotics eventually lead to the selection of resistant organisms. Selection of opportunistic fungi, resistant gram negative rods, *S. epidermidis*, and enterococci is likely. In addition, unless the "delivery" of the antibiotic is rapid, potent, and long lasting, formation of the protective glycocalyx will prevent its effectiveness. In addition, many antibiotics produce allergic reactions in some patients.

The present invention is based on an alternative approach, namely interference with the adherence of bacteria to

polymeric surfaces of medical devices. Studies have demonstrated that both the degree of slime and adhesive production influence and correlate with the degree of bacterial adherence to silastic catheters. *S. haemolyticus*, unlike *S. epidermidis* do not produce slime and are a very uncommon cause of catheter related infection. As described herein, substances that prevent or reduce the production of slime by bacteria reduce their adherence and thus reduce the level of growth of microorganisms on the surface of the inserted or implanted devices.

It has been observed that sodium salicylates and certain other compounds can interfere with the production of capsule polysaccharide production in *Klebsiella pneumoniae*. Salicylate binds to lipids in the outer membrane where biosynthetic enzymes are located. It has been postulated that capsular polysaccharide is the backbone of glycocalyx formation.

An object of the present invention is to use salicylates and other nonsteroidal anti-inflammatory drugs ("NSAID"), as well as other compounds such as chelating agents, to prevent the production of slime or surface polysaccharides in target microorganisms, thereby preventing their adherence and growth on materials used in medical devices.

A further object of the present invention is to utilize slime or surface-polysaccharide-inhibiting compounds which have, in addition, anti-platelet and thrombotic properties. This is particularly useful since the formation of the glycocalyx may be determined in part by platelets and fibronectin. The use of such compounds may decrease the incidence of thrombophlebitis as well as infection.

It is a further objective of the present invention to reduce bacterial growth on implanted devices using compounds that are relatively non-toxic.

These and other objectives are accomplished by the invention described in detail below.

20 SUMMARY OF THE INVENTION

As embodied herein, the foregoing and other objects are achieved by the present invention which involves the use of salicylic acid and other similarly-acting compounds to inhibit the formation of microbial slime or surface polysaccharides, thus interfering with their ability to adhere to invasive medical devices and thereby cause infection.

DETAILED DESCRIPTION OF THE INVENTION

Described herein is a method for preventing the adherence and growth of microorganisms on catheters as well as other insertable or implantable medical devices using slime-inhibiting compounds in an amount being insufficient to produce systemic therapeutic benefits. Reduction of the slime production by such microorganisms reduces their ability to adhere to the medical device thus reducing the risk of infection and nosocomial sepsis.

The present invention is based on the discovery that by inhibiting the adherence of bacteria to catheters and other medically related foreign bodies, the risk of infection and sepsis can be reduced, and the residence time in which the medical device can remain in the body can be increased. The adherence of the bacteria to the medical device is inhibited by using a compound that interferes with the ability of the microorganism to produce a slime. The term slime, as used herein, includes the extracellular and capsular substance, composed to a large extent of extracellular polysaccharide, which is produced by many microorganisms, including coagulase negative staphylococci such as *S. epidermidis* and *S. aureus*, *Escherichia coli*, *pseudomonas* and other gram negative rods, as well as other microorganisms.

A slime-inhibiting compound is a substance or collection of substances which inhibits either production of the slime produced by a microorganism, or a component of the slime, such as the polysaccharide component. Regardless of the component of the slime that it inhibits, the slime-inhibitor reduces the ability of a microorganism to adhere to a polymeric surface. Slime inhibiting compounds include, but are not limited to, NSAID such as acetylsalicylic acid (aspirin), salicylate, bis-salicylate, benzyl-benzoic acid, diflunisal, fendosal, indometacin, acetaminophen, cinmetacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, isoxepac, ibuprofen, flurbiprofen, naproxen, ketoprofen, fenoprofen, benoxaprofen, indoprofen, pirprofen, carprofen, mefenamic acid, flufenamic acid, meclofenamate, niflumic acid, tolfenamic acid, flunixin, clonixin, phenylbutazone, feprazon, apazone, trimethazone, mofebutazone, kebuzone, suxibuzone, piroxicam, isoxicam and tenoxicam, as well as chelating agents.

As contemplated herein, medically implanted or inserted devices include those inserted percutaneously or through an orifice, or implanted for short or long ranges of time as well as permanently. Such devices include catheters as well as sutures, heart valves, grafts such as vascular or other tissue grafts and prosthetic devices such as artificial hips and knees. Such devices are generally made of a polymeric material such as silastic or other silicone-based material, polyethylene terephthalate (PET), dacron, knitted dacron, velour dacron, polyglactin, chromic gut, nylon, silk, bovine arterial graft, polyethylene (PE), polyurethane, polyvinyl chloride, silastic elastomer, silicone rubber, PMMA [poly-(methyl methacrylate)], latex, polypropylene (PP), titanium, cellulose, poly vinyl alcohol (PVA), poly (hydroxyethyl methacrylate) (HEMA), poly (glycolic acid), poly (acrylonitrile) (PAN), fluoroethylene-co-hexafluoropropylene (FEP), teflon (PTFE) and Co-Cr alloys.

The slime inhibitor may be added to the material on which microbial growth is to be inhibited by spraying, dipping, soaking, or by incorporation into the material itself. Alternatively, the inhibitor may be incorporated into a secondary pol-

5 ymer used to coat the surface of the medical device. Such a secondary polymer may have slow release properties that allow for the gradual release of the inhibitor into the microenvironment of the device.

Several of the slime-inhibitors used to practice the present invention have additional therapeutic properties. Accordingly, their use is often suggested in conjunction with medical implants, ostensibly to decrease swelling around the site of implantation. For example, in U.S. 4,769,013 the use of salicylate as an analgesic or anesthetic in conjunction with a medical material is suggested. In addition, drugs described herein have been incorporated into drug delivery devices because of their therapeutic properties. However, the level of compound used in such circumstances must be relatively high to achieve the desired therapeutic result.

In contrast, and because the present invention contemplates use of a level of compound sufficient only to inhibit 10 slime formation within the microenvironment of the device, the levels of the compounds described herein are below the level necessary for therapeutic systemic effect. Generally, the amount of inhibitor utilized herein to prevent production of polysaccharide production and adherence to the device, as measured by concentration on the surface of the device, is between about 1 and about 20mM. This level is believed to be sufficient to decrease the incidence of thrombophlebitis associated with the device due to the known anti-platelet activity of NSAID.

15 According to one preferred embodiment, distribution of the inhibitor on the device to be inserted or implanted is accomplished by incubating the device in a solution containing the slime-inhibitor. The inhibitor is suspended in a solution, most preferably an alcohol-based solution, at a concentration of between about 1 mM and 1 M. The device is incubated within such a solution for between about 15 minutes and 24 hours at a temperature of between about -20°C to 25°C after which it is air dried.

20 Preferably the coating is performed at between about -20°C and 10°C. In general, use of the inhibitor in conjunction with alcohol has been found to increase the polysaccharide inhibiting properties. When the surface to be treated is teflon, however, the alcohol decreases the effectiveness of the slime-inhibitor. When alcohol is used, optimum results are often obtained by incubating at -20°C.

25 Another method makes use of tridodecylemethylammonium chloride (TDMAC) or benzalkonium chloride to bind the slime-inhibiting substance to the catheter or medical device. TDMAC has previously been used to coat catheters and other medical devices with antibiotics and heparin.

The ability of a compound to inhibit the production of slime by a microorganism and thereby inhibit its growth on a 30 medically insertable or implantable device can be measured by several methods. Once the device is coated or impregnated with the compound, the device is exposed to a source of bacteria over a specified period of time, after which the device is washed and the growth of the bacteria on the device measured. Such measurements may include colony counts or other means of quantifying microorganisms, such as chemiluminescent or bioluminescent assay, which monitor a particular metabolite as a means of quantifying bacterial load or by radiolabelling techniques.

A suitable methodology for analyzing the effectiveness of an inhibitor in preventing microbial growth on catheters or other medically insertable or implantable devices is described in Example 21.

35 Although the current application deals with medical devices, this concept can be applied in a number of industrial areas. Glycocalyx formation by gram negative rods occurs in PVC and other plumbing supplies. The formation of this glycocalyx has been shown to contaminate the manufacturing process of products in which sterility is vital. Coating such pipes with a NSAID may minimize this problem.

40 In addition, similar applications can be considered in the marine industry where water-borne organisms cause destruction. Also contemplated by the present invention is the use of the NSAID as additives to waterproofing and coatings for boats and other marine supplies.

EXAMPLES

45 Example 1

The effect of sodium salicylate on the growth characteristics of various organisms was studied. A slime producing strain of coagulase negative staphylococcus was grown in increasing concentrations of salicylate in two different types of media, chemically defined media (CDM) and tripticase soy broth (TSB). The resultant bacterial counts were as follows:

| | CDM | TSB |
|---------|-------------------|-------------------|
| Control | 2.3×10^9 | 1.2×10^9 |
| 1mM | 7.2×10^8 | 1.4×10^9 |
| 5mM | 8.3×10^8 | 5.7×10^8 |
| 10mM | 5.7×10^8 | 5.2×10^8 |
| 25mM | 2.3×10^8 | 3.2×10^7 |

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These studies demonstrated that salicylate does not have antimicrobial properties. It did not inhibit the growth of coagulase negative staphylococci in either chemically defined media or in commercially prepared trypticase soy broth. Similar growth curves were obtained with gram negative rods including *E. coli* and *pseudomonas*.

Example 2

20 As a crude measure of its ability to influence the production of slime, the yield of slime by weight from a one liter broth culture *S. epidermidis* grown in the presence of increasing concentrations of salicylate was used to measure the ability of salicylate to influence the production of slime.

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| Concentration | Yield |
|---------------|--------|
| Control | 86 mg. |
| 1mM | 68 mg. |
| 5mM | 58 mg. |
| 25mM | 47 mg. |

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As noted, the amount of slime decreased with increasing concentrations of salicylate.

Example 3

40 The effect of increasing concentrations of salicylate on the production of slime by *S. epidermidis* was measured by using a spectrophotometric assay. The results were as follows:

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| Concentration (mM) | Optical Density |
|--------------------|-----------------|
| Control | 1.5 |
| 1 mM | 1.4 |
| 2 mM | 1.3 |
| 5 mM | .5 |
| 10 mM | .08 |
| 25 mM | .01 |

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A progressive fall in the optical density with increasing concentrations of salicylate, most evident at 5 mM and above, was observed.

Example 4

Selected strains of slime-producing coagulase negative staphylococci (*S. epidermidis*) were grown in various concentrations of salicylate. After 24 hours growth, various types of catheters were placed in high concentrations of the organisms for 15 minutes. This assay exposed the catheters to a high concentration of organisms for a short period of time. The catheters were washed three times, and rolled onto agar in a standardized manner. The agar plates were incubated overnight, and the number of colonies counted. The percent inhibition of adherence was calculated with the following formula:

$$10 \quad \% \text{ inhibition} = 100 - \frac{(\# \text{ of CFU adhering in salicylate})}{(\# \text{ CFU adhering in control})} \times 100$$

with the following results:

| | Concentration | Adherence (CFU plate) | Inhibition |
|----|---------------|-----------------------|------------|
| 20 | Polyurethane | | |
| | 0 | 229 | |
| | 1 Mm | 236 | N.I. |
| 25 | 2 Mm | 48 | 79% |
| | Teflon | | |
| | 0 | 171 | |
| 30 | 1 mM | 50 | 71% |
| | 5 mM | 22 | 87% |
| | Silastic | | |
| 35 | 0 | 325 | |
| | 1 mM | 265 | 19% |
| | 2 mM | 149 | 54% |
| 40 | 25 mM | 77 | 76% |
| | PVC | | |
| | 0 | 378 | |
| 45 | 1 mM | 157 | 58% |
| | 5 Mm | 85 | 85% |

Example 5

A similar assay to that used in Example 4 was performed using *S. aureus* and *E. coli*. This was done using a silastic catheter. The results were as follows:

| | Concentration | Adherence (CFU/plate) | | Adherence (CFU/plate) | |
|----|---------------|-----------------------|----------|-----------------------|----------|
| | | <i>E. coli</i> | % Inhib. | <i>S. aureus</i> | % Inhib. |
| 55 | 0 | 90 | | 285 | |
| | 1 mM | 32 | 64 | 154 | 46% |
| | 5 mM | .5 | 99 | 112 | 61% |

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This demonstrated an effect with E. coli and S. aureus that was similar to that observed with S. epidermidis.

Example 6

5 Catheter segments were incubated overnight in salicylate and compared to control catheters that were not incubated in salicylate to determine whether the salicylate would coat the polymer surface.

Catheter segments were incubated in 100 mM salicylate overnight at 37°C, pH 7.0. The catheters were then dried, and dipped into a 5×10^5 CFU/ml coagulase negative staphylococci for 15 minutes. All studies were done in triplicate.

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| | Adherence (CFU/plate) | | |
|--------------|-----------------------|------------|--------|
| | Control | Salicylate | Inhib. |
| Silastic | 600 | 317 | 47% |
| Polyurethane | 33 | 20 | 27% |
| Teflon | 35 | 13 | 63% |
| | 17 | 3 | 82% |
| PVC | 85 | 50 | 41% |

25 Example 7

Teflon, PVC, and silastic catheters were incubated in 100 mM salicylate at 37° overnight and were incubated with high concentrations of bacteria (10^7 - 10^8 CFU/ml). After incubation, the catheters were washed three times, then rolled onto agar and incubated. The colonies were counted. The results were as follows:

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| | Teflon | PVC | Silastic |
|----------------------|-------------|------------|------------|
| <u>E. coli</u> | | | |
| Control | 8.0 | 13 | 211 |
| Salicylate | <u>13.0</u> | <u>9</u> | <u>103</u> |
| Inhibition | 0% | 29% | 51% |
| <u>P. aeruginosa</u> | | | |
| Control | 80 | 275 | 59 |
| Salicylate | <u>1</u> | <u>200</u> | <u>3</u> |
| Inhibition | 100% | 27% | 94% |

The inhibition was most obvious with pseudomonas regardless of the type of polymer used. The E. coli did not adhere as well as pseudomonas regardless of the catheter type.

50 Example 8

A study similar to that described in Example 7 was done with a smaller inoculum of (10^5 CFU/ml) of S. aureus with the results as follows:

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| | Adherence CFU/plate) | Inhibition |
|----|----------------------|------------|
| 5 | Teflon | |
| | Control 147 | |
| | Salicylate 54 | 63% |
| 10 | PVC | |
| | Control 192 | |
| | SAL 136 | 30% |
| 15 | Silastic | |
| | Control 296 | |
| | SAL 224 | 24% |

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Example 9

Silastic and polyurethane catheters were incubated in 95% EtOH and 95% EtOH and 200 mM salicylate at pH 7.0 for 2 hours at -20°C. The catheters were air dried and incubated in broth containing 10^5 CFU/ml *S. epidermidis* for 15 minutes at 37°C. The catheters were then washed and rolled onto agar. The results on two identical experiments were as follows:

| Trial 1 | | | |
|---------|------------------|------------|------------|
| | Control | Salicylate | Inhibition |
| 30 | Polyurethane 143 | 91 | 36% |
| | Silastic 461 | 35 | 92% |

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| Trial 2 | | | |
|---------|------------------|------------|------------|
| | Control | Salicylate | Inhibition |
| 40 | Silastic 37 | .67 | 98% |
| | PVC 60 | 50 | 17% |
| 45 | Teflon 19 | 20 | 0% |
| | Polyurethane 138 | 57 | 59% |

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Example 10

Similar experiments to those described in Example 9 were conducted using *E. coli*. A high concentration of organisms (10^6) was used. Catheter segments were incubated for 2 hours in 200 mM salicylate in 95% ethanol. The catheters were dried and placed in the *E. coli* cultures at room temperature. They were allowed to incubate for 18 hours. The results were as follows:

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| Catheter | (CFU/plate) | | |
|--------------|-------------|------------|------------|
| | Control | Salicylate | Inhibition |
| Polyurethane | 77 | 10 | 88% |
| PVC | 21 | 3 | 86% |
| Silastic | 50 | 3 | 96% |

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Example 11

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Silastic catheters prepared as described in Example 9 were incubated in cultures of *S. epidermidis* for three days at 37°C.

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| CFU/plate | | |
|-----------|------------|------------|
| Control | Salicylate | Inhibition |
| 15 | 6 | 60% |

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Example 12

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Silastic catheters prepared as described in Example 9 were incubated in cultures of *E. coli* for three days. (10^5 CFU/ml).

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| CFU/plate | | |
|-----------|------------|------------|
| Control | Salicylate | Inhibition |
| 1400 | 700 | 50% |

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Example 13

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Polyurethane and silastic catheters were soaked overnight in varying concentrations of salicylic acid in ethanol at - 20°C and then exposed to coagulase negative staphylococci and *E. coli* for 4 hours at 37°C. They were washed and rolled as per the protocol described in Example 9.

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Coagulase Negative Staphylococci (Polyurethane - tubing)

| | pH | Count/Plate | CFU/mm |
|------------------|------|-------------|--------|
| Control | 7.33 | >400 | 20.0 |
| Salicylate 200mM | 7.19 | 310 | 14.6 |
| Salicylate 600mM | 6.77 | 50 | 2.4 |
| Ibuprofen 400mM | 7.22 | 233 | 11.5 |
| Ibuprofen 200mM | 7.02 | 352 | 18.1 |

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| <i>E. coli</i> (silastic tubing) | | |
|----------------------------------|-------------|--------|
| | Count/Plate | CFU/mm |
| Control | 250 | 12.0 |
| Salicylate 200mM | 226 | 11.6 |
| Salicylate 600mM | 32 | 1.6 |
| Ibuprofen 400mM | 238 | 12.0 |
| Ibuprofen 200mM | 185 | 9.6 |

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Example 14

20 Catheters treated with salicylate and ibuprofen as described in Example 9 were incubated in phosphate buffered saline having a concentration of 10^3 CFU/ml *E. coli* for six days at 37°C. This produced a constant concentration of organisms.

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| Coating | (CFU/plate) | Inhibition |
|-------------------|-------------|------------|
| Control | 240 | |
| 200 mM salicylate | 121 | 50% |
| 100 mM Ibuprofen | 70 | 71% |

Despite six days of incubation, the inhibition was impressive. It was greater with ibuprofen than salicylate in this experiment.

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Example 15

40 Polyurethane and silastic catheters were incubated in ibuprofen, acetyl-salicylate, and benzoylbenzoic acid with 95% ethanol for 2 hours. The catheters were then incubated in *S. epidermidis* as described in Example 9. The results were as follows:

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| Polyurethane | CFU/plate) | Inhibition |
|---------------------------|------------|------------|
| Control | 295 | |
| Acetyl-Salicylate (200mM) | 127 | 57% |
| Salicylate (200mM) | 270 | 9% |
| Ibuprofen (100mM) | 166 | 44% |
| Benzyl benzoic (100mM) | 333 | 0% |
| Silastic | | |
| Control | 52 | |
| Acetyl-Salicylate (200mM) | 7 | 86% |
| Salicylate (200mM) | 33 | 36% |
| Benzyl benzoic (100mM) | 9 | 83% |

Example 16

5 Polyurethane catheters were preheated overnight at 67°C and coated in the compounds listed below at -20°C in 95% ethanol. They were then incubated in coagulase negative staphylococci at 37° for 18 hours, and washed three times in phosphate buffered saline. ATP was extracted with extralight and read with firelight in a dynatech luminometer reader.

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| | Units of light (measured at 48°) |
|------------------|----------------------------------|
| Control | .62 |
| Salicylate | .19 |
| Acetylsalicylate | .06 |
| Acetaminophen | 2.4 |
| Ibuprofen | .32 |
| Phenylbutazone | .02 |
| Indomethacin | .07 |

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The units of light are a reflection of the amount of ATP released and bacteria that have adhered to the polymer. The experiment was repeated, but by growing the organisms directly in the microlite wells. Cultures of coagulase negative staphylococci were grown in the presence of 2mM NSAID in microlite wells, washed and treated with extralight and fire-light.

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| | Units of light (measured at 48°) |
|------------------|----------------------------------|
| Control | 89.0 |
| Acetylsalicylate | 13.0 |
| Salicylate | 15.0 |
| Ibuprofen | 9.0 |
| Acetaminophen | 108.0 |
| Indomethacin | 9.2 |
| Phenylbutazone | 19.1 |

Example 17

50 Several experiments were done with gram negative rods in urine instead of broth. Silastic catheters were prepared as previously described and were incubated for 4-5 hours at 37°C. All studies were done in triplet.

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| E. coli Incubated in Urine (5 Hours) | | |
|--------------------------------------|--------|------------|
| Silastic Catheter | CFU/mM | Inhibition |
| Control | 25.0 | |
| Salicylic Acid (200mM) | 17.0 | 31% |
| Salicylic Acid (600mM) | 1.5 | 94% |

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| Klebsiella pneumoniae (4 Hours) | | |
|---------------------------------|--------|------------|
| Silastic Catheter | CFU/mM | Inhibition |
| Control | 14.0 | |
| Salicylic Acid (200mM) | 4.9 | 65% |
| Salicylic Acid (600mM) | 1.8 | 87% |

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| E. Aerogenes in Urine (5 Hours) | | |
|---------------------------------|--------|------------|
| Silastic Catheter | CFU/mM | Inhibition |
| Control | 15.5 | |
| Salicylic Acid (200mM) | 9.8 | 37% |
| Salicylic Acid (600mM) | 4.3 | 73% |

Example 18

40 In an attempt to determine the length of the observed effect, silastic catheters were incubated in salicylic acid as described, and then placed in sterile urine for 4 days. At the end of this period, the catheters were removed and then placed in a broth culture of *E. coli*. Results are the mean of three trials.

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| Silastic Catheter | CFU/mM | Inhibition |
|------------------------|--------|------------|
| Control | 13.2 | |
| Salicylic Acid (200mM) | 9.6 | 27% |
| Salicylic Acid (600mM) | 2.9 | 78% |

This experiment demonstrated that the coating is not lost immediately after the catheter is placed in an aqueous solution.

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Example 19

S. epidermidis was radiolabeled by including 1 μ Ci of (14 C - sodium acetate) in the preliminary overnight culture. The catheter segments were exposed to the broth culture overnight at 37°C. The catheters were vigorously washed in

saline, air dried, and placed in scintillation vials for counting.

| TSB with NaAc (1.2 - ^{14}C) Overnight at 37°C | |
|---|--------|
| Silastic Catheter | CPM |
| Control | 1481.0 |
| Salicylic Acid (200mM) | 528.0 |
| Salicylic Acid (600mM) | 165.0 |

15 Example 20

Another embodiment uses tridodecylmethyammonium chloride (TDMAC) or benzalkonium chloride which coats the catheters and also binds to the salicylates. Silastic catheters that had been preheated were coated in 5% TDMAC in ethanol for 40 minutes at room temperature. The catheter segments were vigorously washed with sterile water and air dried. The segments were then immersed in ethanol, 200mM salicylic acid and 600mM salicylic acid overnight at -20°C. The catheters were air dried and immersed in a trypticase soy broth culture of *E. coli* or *S. epidermidis* at 37°C. Catheters were washed 3 times in 3 changes of sterile saline and rolled on Mueller-Hinton Agar plates. The plates were incubated overnight at 37°C and the colonies were counted.

| | | CFU/Plate | CFU/mM | Inhibition | |
|----|------------------------------------|---|----------------------|--------------------|------------|
| 30 | <i>E. coli</i> (5 Hour Incubation) | Control Salicylic Acid (200mM) Salicylic ACid (600mM) | 143.0 23.0 1.5 | 6.5 1.1 0.07 | 83% 99% |

| | | CFU/Plate | CFU/mM | Inhibition | |
|----|--|---|----------------------|-------------------|-----------|
| 40 | <i>S. epidermidis</i> (Overnight Incubation) | Control Salicylic Acid (200mM) Salicylic Acid (600mM) | 91.0 81.0 52.0 | 4.3 3.9 2.6 | 9% 40% |

45 Example 21

The following is a recommended method for determining whether a particular compound inhibits slime production and adherence to a medical device:

50 1. Prepare test coating solutions at desired concentrations. Prepare sterile 3 cm section of tubing.
 2. Incubate tubing pieces in sterile water at 67°C overnight, dry 1 hour, then expose to test solutions and controls at -20°C for 2 hours. Ensure that all tubing are immersed in solution.
 3. Remove the tubing and dry coated samples in a sterile field. Mark tubing 1 cm from end.
 4. Assemble a sterile 3 cm syringe with a sterile industrial blunt syringe which will fit securely into the tubing to be tested.
 5. Attach the marked end of the 3 cm lengths of coated tubing to the needle. Withdraw the plunger from the syringe to about the 2 or 3 cc mark.
 6. Place 15 ml of a 10^6 bacterial suspension into a sterile 50 cc tube and place up to 3 tubes into each tube. Incu-

bate at 37°C for 15 minutes. The length of incubation and inoculum size can be varied.

7. Transfer each tubing segment into a separate 15 ml sterile tube containing approximately 5 ml of sterile saline.

Each tube is vigorously washed by drawing saline back and forth through the tube 3 times.

8. The process is repeated until a total of 3 washes in 3 separate saline tubes is completed.

5 9. A 1 cm segment of the distal catheter is cut off and discarded.

10. The remaining 2 cm section was quantitatively rolled over a blood agar plate in 4 directions. The plates are incubated overnight at 37°C and the colonies are counted.

11. The catheter segments are carefully measured so that the number of CFU/mm catheter can be calculated.

10 **Claims**

1. A method of reducing infection associated with an implantable or insertable medical device comprising distributing on said device a slime-inhibiting effective amount of a slime-inhibiting compound, said effective amount being insufficient to produce systemic therapeutic benefits.

15 2. A method according to claim 1 wherein said slime-inhibiting compound is a chelating agent.

3. A method according to claim 1 wherein said slime-inhibiting compound is a NSAID.

20 4. A method according to claim 3 wherein said NSAID is selected from the group consisting of salicylic acid, acetyl-salicylic acid (aspirin), bis-salicylate, benzyl-benzoic acid, diflunisal, fendosal, indomethacin, acemetacin, cinmetacin, sulindac, tolmetin zomepirac, diclofenac, fenclofenac, isoxepac, ibuprofen, flurbiprofen, naproxen, Xetoprofen, fenoprofen, benoxaprofen, indoprofen, pirprofen, carprofen, mefenamic acid, flufenamic acid, meclofenamate, niflumic acid, tolfenamic acid, flunixin, clonixin, phenylbutazone, feprazole, apazone, trimethazone, mofebutazone, kebuzone, suxibuzone, piroxicam, isoxicam and tenoxicam.

25 5. A method according to claim 4 wherein said NSAID is salicylic acid or sodium salicylate.

6. A method according to claim 4 wherein said NSAID is ibuprofen.

30 7. A method according to claim 1 wherein said slime-inhibiting compound is distributed on the medical device by incorporating it into the medical material during manufacture of said material.

8. A method according to claim 1 wherein said slime-inhibiting compound is distributed on said device using TDMAC or benzalkonium chloride.

35 9. A method according to claim 1 wherein said slime-inhibiting compound is distributed on said device by soaking the device in a solution containing the slime-inhibiting compound.

40 10. A method according to claim 9 wherein the concentration of the slime-inhibiting compound in said solution is between about 1 and about 1 M.

11. A method according to claim 9 wherein said soaking is conducted for between about 10 minutes and about 24 hours.

45 12. A method according to claim 9 wherein the solution is alcohol based.

13. A method according to claim 11 wherein said alcohol consists essentially of ethanol.

50 14. A method according to claim 9 wherein said soaking is conducted at between about -20° and 25°C.

15. A method according to claim 13 wherein said soaking is conducted at refrigerated temperatures.

16. A method according to claim 13 wherein said soaking is conducted at about -20°C.

55 17. A method according to claim 9 wherein said soaking results in incorporation of slime-inhibiting compound into the medical device material.

18. A method according to claim 1 wherein said device is made of a polymer selected from the group consisting of

silastic or other silicone-based material, polyethylene terephthalate (PET), polyglacgin, polydioxanone, chromic gut, nylon, silk, dacron, knitted dacron, velour dacron, bovine arterial graft, polyethylene (PE), polyvinyl chloride (PVC), silastic elastomer, silicone rubber, PMMA [poly-(methyl methacrylate)], latex, polypropylene (PP), titanium, cellulose, polyvinyl alcohol (PVA), poly-(hydroxyethyl methacrylate) (PHEMA), poly-(glycolic acid), poly (acrylonitrile) (PAN), fluoroethylene-co-hexafluoropropylene (FEP), teflon (PTFE), Co-Cr alloys, PVC, polyurethane, polyester, polytetrafluoroethylene, and biological polymers such as collagen.

5 19. A method according to claim 1 wherein said slime-inhibiting compound is distributed by coating the device with a polymer containing the slime-inhibiting compound.

10 20. A method according to claim 19 wherein said polymer has slow release properties.

15 21. A method according to claim 1 wherein said effective amount of slime-inhibiting compound on or near the surface of the device is between about 1 and about 20 mM.

20 22. A method according to claim 1 wherein said slime-inhibiting compound is distributed on said device by a method comprising:

25 exposing said medical device, prior to insertion or implantation, in a solution, said solution having a concentration of between about 1 mM and about 1 M of the slime-inhibiting compound;

30 removing said medical device from said solution;

35 drying said medical device; and

40 wherein said medical device is inserted or implanted in a mammal.

25 23. A method according to claim 1 wherein the effective amount of said compound is distributed on said medical device by a method comprising:

30 coating said medical device, prior to insertion or implantation, with a polymer, said polymer having a concentration of between about 1 mM and about 1 M of a slime-inhibiting compound to thereby inhibit the growth of microorganisms on said medical device upon implantation or insertion of said medical device; and wherein said medical device is implanted or inserted in a mammal.

45 24. A method according to claim 23 wherein said polymer has slow release properties.

50 25. A method according to claim 24 wherein said polymer is selected from the group consisting of silastic or other silicone-based material, polyethylene terephthalate (PET), polyglacgin, polydioxanone, chromic gut, nylon, silk, dacron, knitted dacron, velour dacron, bovine arterial graft, polyethylene (PE), polyvinyl chloride (PVC), silastic elastomer, silicone rubber, PMMA [poly-(methyl methacrylate)], latex, polypropylene (PP), titanium, cellulose, polyvinyl alcohol (PVA), poly(hydroxyethyl methacrylate) (PHEMA), poly-(glycolic acid), poly (acrylonitrile) (PAN), fluoroethylene-co-hexafluoropropylene (FEP), teflon (PTFE), Co-Cr alloys, PVC, polyurethane, polyester, polytetrafluoroethylene, and biological polymers such as collagen.

55 26. A method according to claim 1 wherein the effective amount of said compound is distributed on said medical device by a method comprising exposing said device, prior to insertion or implantation, with said slime-inhibiting compound, said exposure being sufficient to coat the device with an amount of inhibiting compound capable of reducing the amount of microbial growth on said device upon implantation, but being at an amount insufficient to produce systemic therapeutic benefits.

60 27. A method according to claim 26 wherein said device is a catheter.

65 28. A method according to claim 1 wherein the effective amount of said slime-inhibiting compound is a thrombophlebitis-reducing effective amount of a NSAID.

70 29. A method according to claim 28 wherein said NSAID is selected from the group consisting of salicylic acid, acetyl-salicylic acid (aspirin), bis-salicylate, benzyl-benzoic acid, diflunisal, fendosal indomethacin, acetaminophen, cinmetacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, isoxepac, ibuprofen, flurbiprofen, naproxen, ketoprofen, fenoprofen, benoxaprofen, indoprofen, pirprofen, carprofen, mefenamic acid, flufenamic acid, meclofenamate, niflumic acid, tolafenamic acid, flunixin, clonixin, phenylbutazone, feprazon, apazone, trimethazone, mofebutazone, kebuzone, suxibuzone, piroxicam, isoxicam and tenoxicam.

30. An insertable or implantable medical device having reduced risk of causing infection after insertion or implantation comprising a device having distributed thereon a slime-inhibiting effective amount of a slime-inhibiting compound, said effective amount being insufficient to produce systemic therapeutic benefits.

5 31. A device according to claim 30 wherein said slime inhibiting compound is present at a level of between about 1 and about 20mM.

10 32. A device according to claim 30 wherein said device is comprised of a polymer selected from the group consisting of silastic or other silicone-based material, polyethylene terephthalate (PET), polyglacgin, polydioxanone, chromic gut, nylon, silk, dacron, knitted dacron, velour dacron, bovine arterial graft, polyethylene (PE), polyvinyl chloride (PVC), silastic elastomer, silicone rubber, PMMA [poly-(methyl methacrylate)], latex, polypropylene (PP), titanium, cellulose, polyvinyl alcohol (PVA), poly-(hydroxyethyl methacrylate) (PHEMA), poly-(glycolic acid), poly (acrylonitrile) (PAN), floroethylene-co-hexafluoropropylene (FEP), teflon (PTFE), Co-cr alloys, PVC, polyurethane, polyester, polytetrafluoroethylene, and biological polymers such as collagen.

15 33. A device according to claim 30 wherein said slime-inhibiting compound is a chelating agent.

34. A device according to claim 30 wherein said slime-inhibiting compound is a NSAID.

20 35. A device according to claim 34 wherein said NSAID is selected from the group consisting of salicylic acid, acetyl-salicylic acid (aspirin), bis-salicylate, benzyl-benzoic acid, diflunisal, fendosal, indomethacin, acemetacin, cinmetacin, sulindac, tolmetin, zomepirac, diclofenac, isoxepac, ibuprofen, flurbiprofen, naproxen, ketoprofen, fenoprofen, benoxaprofen, indoprofen, pirprofen, carprofen, mefenamic acid, flufenamic acid, meclofenamate, niflumic acid, tolafenamic acid, flunixin, clonixin, phenylbutazone, feprazon, apazone, trimethazone, mofebutazone, kebuzone, suxibuzone, piroxicam, isoxicam and tenoxicam.

25 36. A device according to claim 35 wherein said NSAID is salicylic acid or a salt thereof.

30 37. A device according to claim 35 wherein said NSAID is ibuprofen.

38. An insertable or implantable medical device according to claim 30 wherein the effective amount of said slime-inhibiting compound is a thrombophlebitis-reducing effective amount of a NSAID.

39. A device according to claim 38 wherein said NSAID is present at a level of between about 1 and about 20mM.

35 40. A device according to claim 38 wherein said NSAID is selected from the group consisting of salicylic acid, acetyl-salicylic acid (aspirin), bis-salicylate, benzyl-benzoic acid, diflunisal, fendosal, indomethacin, acemetacin, cinmetacin, sulindac, tolmetin, zomepirac, diclofenac, isoxepac, ibuprofen, flurbiprofen, naproxen, ketoprofen, fenoprofen, benoxaprofen, indoprofen, pirprofen, carprofen, mefenamic acid, flufenamic acid, meclofenamate, niflumic acid, tolafenamic acid, flunixin, clonixin, phenylbutazone, feprazon, apazone, trimethazone, mofebutazone, kebuzone, suxibuzone, piroxicam, isoxicam and tenoxicam.

Patentansprüche

45 1. Verfahren zur Verminderung der Infektion, die mit einer implantierbaren oder einsetzbaren medizinischen Einrichtung verbunden ist, das umfaßt das Verteilen einer die Schleimbildung inhibierenden wirksamen Menge einer Schleim-inhibierenden Verbindung auf der genannten Einrichtung, wobei die genannte wirksame Menge nicht ausreicht, um systemische therapeutische Vorteile zu ergeben.

50 2. Verfahren nach Anspruch 1, worin die genannte Schleim-inhibierende Verbindung ein Chelatbildner ist.

3. Verfahren nach Anspruch 1, worin die genannte Schleim-inhibierende Verbindung ein NSAID ist.

55 4. Verfahren nach Anspruch 3, worin das genannte NSAID ausgewählt wird aus der Gruppe, die besteht aus Salicylsäure, Acetylsalicylsäure (Aspirin), Bis-salicylat, Benzylbenzoësäure, Diflunisal, Fendosal, Indomethacin, Acemetacin, Cinmetacin, Sulindac, Tolmetin, Zomepirac, Diclofenac, Fenclofenac, Isoxepac, Ibuprofen, Flurbiprofen, Naproxen, Xetoprofen, Fenoprofen, Benoxaprofen, Indoprofen, Pirprofen, Carprofen, Mefenamsäure, Flufenamsäure, Meclofenamat, Niflumsäure, Tolfenamsäure, Flunixin, Clonixin, Phenylbutazon, Feprazon, Apazon, Trimethazon, Mofebutazon, Kebuzon, Suxibuzon, Piroxicam, Isoxicam und Tenoxicam.

5. Verfahren nach Anspruch 4, worin das genannte NSAID Salicilsäure oder Natriumsalicylat ist.
6. Verfahren nach Anspruch 4, worin das genannten NSAID Ibuprofen ist.
- 5 7. Verfahren nach Anspruch 1, worin die genannte Schleim-inhibierende Verbindung auf der medizinischen Einrichtung verteilt wird durch Einarbeitung derselben in das medizinische Material während der Herstellung des genannten Materials.
- 10 8. Verfahren nach Anspruch 1, worin die genannte Schleim-inhibierende Verbindung auf der genannten Einrichtung unter Verwendung von TDMAC oder Benzalkoniumchlorid verteilt wird.
9. Verfahren nach Anspruch 1, worin die genannte Schleim-inhibierende Verbindung auf der genannten Einrichtung verteilt wird durch Eintauchen der Einrichtung in eine Lösung, welche die Schleim-inhibierende Verbindung enthält.
- 15 10. Verfahren nach Anspruch 9, worin die Konzentration der Schleim-inhibierenden Verbindung in der genannten Lösung zwischen etwa 1 mM und etwa 1 M liegt.
11. Verfahren nach Anspruch 9, worin das genannte Eintauchen für einen Zeitraum zwischen etwa 10 min und etwa 24 h durchgeführt wird.
- 20 12. Verfahren nach Anspruch 9, worin die Lösung eine solche auf Alkoholbasis ist.
13. Verfahren nach Anspruch 11, worin der Alkohol im wesentlichen aus Ethanol besteht.
- 25 14. Verfahren nach Anspruch 9, worin das genannte Eintauchen bei einer Temperatur zwischen etwa -20° und 25°C durchgeführt wird.
15. Verfahren nach Anspruch 13, worin das genannte Eintauchen bei Einfriertemperaturen durchgeführt wird.
- 30 16. Verfahren nach Anspruch 13, worin das genannte Eintauchen bei etwa -20°C durchgeführt wird.
17. Verfahren nach Anspruch 9, worin das genannte Eintauchen zur Einarbeitung der Schleim-inhibierenden Verbindung in das Material der medizinischen Einrichtung führt.
- 35 18. Verfahren nach Anspruch 1, worin die genannte Einrichtung hergestellt wird aus einem Polymer, das ausgewählt wird aus der Gruppe, die besteht aus silastischem Material oder einem anderen Material auf Siliconbasis, Polyethylenterephthalat (PET), Polyglycin, Polydioxanon, Chromdarm (chromic gut), Nylon, Seide, Dacron, gewirktem Dacron, Velour-Dacron, Rinderarterien-Transplantat, Polyethylen (PE), Polyvinylchlorid (PVC), einem silastischen Elastomeren, Siliconkautschuk, PMMA [Poly-(methylmethacrylat)], Latex, Polypropylen (PP), Titan, Cellulose, 40 Polyvinylalkohol (PVA), Poly(hydroxyethylmethacrylat) (HEMA), Poly(glycolsäure), Poly(acrylnitril) (PAN), Fluoroethylen-co-hexafluoropropen (FEP), Teflon (PTFE), Co-Cr-Legierungen, PVC, Polyurethan, Polyester, Polytetrafluoroethylen und biologischen Polymeren wie Collagen.
19. Verfahren nach Anspruch 1, worin die genannte Schleim-inhibierende Verbindung durch Beschichten der Einrichtung mit einem Polymer, das die Schleim-inhibierende Verbindung enthält, verteilt wird.
- 45 20. Verfahren nach Anspruch 19, worin das genannte Polymer langsame Freisetzungseigenschaften aufweist.
21. Verfahren nach Anspruch 1, worin die genannte wirksame Menge der Schleim-inhibierenden Verbindung auf oder 50 in der Nähe der Oberfläche der Einrichtung zwischen etwa 1 und etwa 20 mM liegt.
22. Verfahren nach Anspruch 1, worin die genannte Schleim-inhibierende Verbindung auf der genannten Einrichtung nach einem Verfahren verteilt wird, das umfaßt:
 - 55 das Einführen der genannten medizinischen Einrichtung vor dem Einsetzen oder vor dem Implantieren in eine Lösung, die eine Konzentration der Schleim-inhibierenden Verbindung zwischen etwa 1 mM und etwa 1 M aufweist;
 - die Entnahme der genannten medizinischen Einrichtung aus der genannten Lösung;
 - das Trocknen der genannten medizinischen Einrichtung; und

das Einsetzen oder Implantieren der genannten medizinischen Einrichtung in ein Säugetier.

23. Verfahren nach Anspruch 1, worin die wirksame Menge der genannten Verbindung auf der genannten medizinischen Einrichtung nach einem Verfahren verteilt wird, das umfaßt:

5

das Beschichten der genannten medizinischen Einrichtung vor dem Einsetzen oder Implantieren mit einem Polymer, das eine Schleim inhibierende Verbindung in einer Konzentration zwischen etwa 1 mM und etwa 1 M aufweist, um dadurch das Wachstum von Mikroorganismen auf der genannten medizinischen Einrichtung beim Implantieren oder Einsetzen der genannten medizinischen Einrichtung zu verhindern, und
10 das Einsetzen oder Implantieren der genannten medizinischen Einrichtung in ein Säugetier.

24. Verfahren nach Anspruch 23, worin das genannte Polymer langsame Freisetzungseigenschaften aufweist.

25. Verfahren nach Anspruch 24, worin das genannte Polymer ausgewählt wird aus der Gruppe, die besteht aus silastischem oder einem anderen Material auf Siliconbasis, Polyethylenterephthalat (PET), Polyglycin, Polydioxanon, Chromdarm (chromic gut), Nylon, Seide, Dacron, gewirktem Dacron, Velour-Dacron, Rinderarterien-Transplantat, Polyethylen (PE), Polyvinylchlorid (PVC), einem silastischen Elastomeren, Siliconkautschuk, PMMA [Poly-(methylmethacrylat)], Latex, Polypropylen (PP), Titan, Cellulose, Polyvinylalkohol (PVA), Poly(hydroxyethylmethacrylat) (PHEMA), Poly(glycolsäure), Poly(acrylnitril) (PAN), Fluoroethylen-co-hexafluoropropyl (FEP), Teflon (PTFE),
20 Co-Cr-Legierungen, PVC, Polyurethan, Polyester, Polytetrafluoroethylen und biologischen Polymeren wie Collagen.

26. Verfahren nach Anspruch 1, worin die wirksame Menge der genannten Verbindung auf der medizinischen Einrichtung unter Anwendung eines Verfahrens verteilt wird, das umfaßt das Einwirkenlassen der genannten Schleim inhibierenden Verbindung auf die genannte Einrichtung vor dem Einsetzen oder Implantieren derselben, wobei das genannte Einwirkenlassen ausreicht, um die Einrichtung mit einer Menge an Schleim inhibierender Verbindung zu überziehen, die in der Lage ist, die Menge des mikrobiellen Wachstums auf der genannten Einrichtung bei der Implantation zu vermindern, die jedoch nicht ausreichend ist, um systemische therapeutische Vorteile zu ergeben.
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27. Verfahren nach Anspruch 26, worin die genannte Einrichtung ein Katheter ist.

28. Verfahren nach Anspruch 1, worin die wirksame Menge der genannten Schleim-inhibierenden Verbindung eine die Thrombophlebitis vermindernde wirksame Menge eines NSAID ist.

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29. Verfahren nach Anspruch 28, worin das genannte NSAID ausgewählt wird aus der Gruppe, die besteht aus Salicylsäure, Acetylsalicylsäure (Aspirin), Bis-salicylat, Benzylbenzoësäure, Diflunisal, Fendosal, Indometacin, Ace-metacin, Cinmetacin, Sulindac, Tolmetin, Zomepirac, Diclofenac, Fenclofenac, Isoxepac, Ibuprofen, Flurbiprofen, Naproxen, Ketoprofen, Fenoprofen, Benoxaprofen, Indoprofen, Pirprofen, Carprofen, Mefenamsäure, Flufenamsäure, Meclofenamat, Niflumsäure, Tolfensäure, Flunixin, Clonixin, Phenylbutazon, Feprazon, Apazon, Trime-thazon, Mofebutazon, Kebuzon, Suxibuzon, Piroxicam, Isoxicam und Tenoxicam.
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30. Einsetzbare oder implantierbare medizinische Einrichtung mit einer geringeren Gefahr der Veursachung einer Infektion nach dem Einsetzen oder Implantieren, die umfaßt eine Einrichtung, auf der eine für die Schleiminhibierung wirksame Menge einer Schleim-inhibierenden Verbindung verteilt ist, wobei die genannte wirksame Menge nicht ausreicht, um systemische therapeutische Vorteile zu ergeben.

31. Einrichtung nach Anspruch 30, in der die genannte Schleiminhibierende Verbindung in einer Menge zwischen etwa 1 und etwa 20 mM vorliegt.

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32. Einrichtung nach Anspruch 30, bei der die genannte Einrichtung besteht aus einem Polymer, ausgewählt aus der Gruppe, die besteht aus einem silastischen Material oder einem anderen Material auf Siliconbasis, Polyethylenterephthalat (PET), Polyglycin, Polydioxanon, Chromdarm (chromic gut), Nylon, Seide, Dacron, gewirktem Dacron, Velour-Dacron, Rinderarterien-Transplantat, Polyethylen (PE), Polyvinylchlorid (PVC), einem silastischen Elastomeren, Siliconkautschuk, PMMA [Poly-(methylmethacrylat)], Latex, Polypropylen (PP), Titan, Cellulose, Polyvinylalkohol (PVA), Poly(hydroxyethylmethacrylat) (PHEMA), Poly(glycolsäure), Poly(acrylnitril) (PAN), Fluoroethylen-co-hexafluoropropyl (FEP), Teflon (PTFE), Co-Cr-Legierungen, PVC, Polyurethan, Polyester, Polytetrafluoroethylen und biologischen Polymeren wie Collagen.
55

33. Einrichtung nach Anspruch 30, worin die genannte Schleim-inhibierende Verbindung ein Chelatbildner ist.

34. Einrichtung nach Anspruch 30, worin die genannte Schleim-inhibierende Verbindung ein NSAID ist.

35. Einrichtung nach Anspruch 34, worin die genannte NSAID ausgewählt wird aus der Gruppe, die besteht aus Salicylsäure, Acetylsalicylsäure (Aspirin), Bis-salicylat, Benzylbenzoësäure, Diflunisal, Fendosal, Indomethacin, Acemetacin, Cinmetacin, Sulindac, Tolmetin, Zomepirac, Diclofenac, Fenclofenac, Isoxepac, Ibuprofen, Flurbiprofen, Naproxen, Ketoprofen, Fenoprofen, Benoxaprofen, Indoprofen, Pirprofen, Carprofen, Mefenamsäure, Flufenamsäure, Meclofenamat, Niflumsäure, Tolfenamsäure, Flunixin, Clonixin, Phenylbutazon, Feprazon, Apazon, Trimethazon, Mofebutazon, Kebuzon, Suxibuzon, Piroxicam, Isoxicam und Tenoxicam.

10 36. Einrichtung nach Anspruch 35, worin das genannte NSAID Salicylsäure oder ein Salz davon ist.

37. Einrichtung nach Anspruch 35, worin das genannte NSAID Ibuprofen ist.

15 38. Einsetzbare oder implantierbare medizinische Einrichtung nach Anspruch 30, in der die wirksame Menge der genannten Schleim-inhibierenden Verbindung eine die Thrombophlebitis vermindernnde wirksame Menge eines NSAID ist.

20 39. Einrichtung nach Anspruch 38, inn der das genannte NSAID in einer Menge zwischen etwa 1 und etwa 20 mM vorliegt.

40. Einrichtung nach Anspruch 38, worin das genannte NSAID ausgewählt wird aus der Gruppe, die besteht aus Salicylsäure, Acetylsalicylsäure (Aspirin), Bis-salicylat, Benzylbenzoësäure, Diflunisal, Fendosal, Indomethacin, Acemetacin, Cinmetacin, Sulindac, Tolmetin, Zomepirac, Diclofenac, Fenclofenac, Isoxepac, Ibuprofen, Flurbiprofen, Naproxen, Ketoprofen, Fenoprofen, Benoxaprofen, Indoprofen, Pirprofen, Carprofen, Mefenamsäure, Flufenamsäure, Meclofenamat, Niflumsäure, Tolfenamsäure, Flunixin, Clonixin, Phenylbutazon, Feprazon, Apazon, Trimethazon, Mofebutazon, Kebuzon, Suxibuzon, Piroxicam, Isoxicam und Tenoxicam.

Revendications

30 1. Procédé pour réduire l'infection liée à un dispositif médical pouvant être implanté ou inséré, comprenant la répartition sur ledit dispositif d'une quantité, efficace pour inhiber la couche visqueuse, d'un composé inhibant la couche visqueuse, ladite quantité efficace étant insuffisante pour avoir des effets favorables thérapeutiques systémiques.

2. Procédé selon la revendication 1, dans lequel ledit composé inhibant la couche visqueuse est un agent chélateur.

35 3. Procédé selon la revendication 1, dans lequel ledit composé inhibant la couche visqueuse est un anti-inflammatoire non stéroïdien (AINS) ("NSAID").

4. Procédé selon la revendication 3, dans lequel ledit AINS est choisi dans le groupe constitué par l'acide salicylique, l'acide acétylsalicylique (Aspirine), le bis-salicylate, l'acide benzylbenzoïque, le diflunisal, le fendosal, l'indométhacine, l'acémétacine, la cinnémétacine, le sulindac, la tolmétine, le zomépirac, le diclofénac, le fenclofénac, l'isoxépac, l'ibuprofène, le flurbiprofène, le naproxène, le kétoprofène, le fénoxaprofène, l'indoprofène, le pirprofène, le carprofène, l'acide méfénamique, l'acide flufenamique, le méclofénamate, l'acide niflumique, l'acide tolfénamique, la flunixinne, la clonixinne, la phénylbutazone, la féprazole, l'apazone, la triméthazone, la mofébutazone, la kébuzone, la suxibuzone, le piroxicam, l'isoxicam et le ténoxicam.

45 5. Procédé selon la revendication 4, dans lequel ledit AINS est l'acide salicylique ou le salicylate de sodium.

6. Procédé selon la revendication 4, dans lequel ledit AINS est l'ibuprofène.

50 7. Procédé selon la revendication 1, dans lequel ledit composé inhibant la couche visqueuse est réparti sur le dispositif médical en l'incorporant dans le matériau médical pendant la fabrication dudit matériau.

8. Procédé selon la revendication 1, dans lequel ledit composé inhibant la couche visqueuse est réparti sur ledit dispositif à l'aide de TDMAC (chlorure de tridodécylméthylammonium) ou de chlorure de benzalconium.

55 9. Procédé selon la revendication 1, dans lequel ledit composé inhibant la couche visqueuse est réparti sur ledit dispositif par immersion du dispositif dans une solution contenant le composé inhibant la couche visqueuse.

10. Procédé selon la revendication 9, dans lequel la concentration du composé inhibant la couche visqueuse dans ladite solution est comprise entre environ 1 nM et environ 1 M.

5 11. Procédé selon la revendication 9, dans lequel ladite immersion est effectuée pendant environ 10 minutes et environ 24 heures.

12. Procédé selon la revendication 9, dans lequel la solution est à base d'alcool.

13. Procédé selon la revendication 11, dans lequel ledit alcool consiste essentiellement en de l'éthanol

10 14. Procédé selon la revendication 9, dans lequel ladite immersion est effectuée à une température comprise entre environ -20 et +25°C.

15 15. Procédé selon la revendication 13, dans lequel ladite immersion est effectuée à des températures obtenues par réfrigération.

16. Procédé selon la revendication 13, dans lequel ladite immersion est effectuée à environ -20°C.

17. Procédé selon la revendication 9, dans lequel ladite immersion a pour résultat l'incorporation du composé inhibant la couche visqueuse dans le matériau du dispositif médical.

20 18. Procédé selon la revendication 1, dans lequel ledit dispositif est fait d'un polymère choisi dans le groupe constitué par un matériau "silastique" ou autre matériau à base de silicium, le poly(téréphthalate d'éthylène) (PET), la polyglycine, la polydioxanone, le catgut chromé, le Nylon, la soie, le Dacron, le Dacron tricoté, le Dacron velours, une greffe artérielle bovine, le polyéthylène (PE), le poly(chlorure de vinyle) (PVC), un élastomère "silastique", un caoutchouc silicium, le PMMA [poly(méthacrylate de méthyle)], le latex, le polypropylène (PP), le titane, la cellulose, le poly(alcool vinylique) (PVA), le poly(méthacrylate d'hydroxyéthyle) (PHEMA), le poly(acide glycolique), le polyacrylonitrile (PAN), un copolymère fluoroéthylène/hexafluoropropylène (FEP), le Téflon (PTFE), des alliages Co-Cr, le PVC, un polyuréthane, un polyester, le polytétrafluoroéthylène et des polymères biologiques tels que le collagène.

30 19. Procédé selon la revendication 1, dans lequel ledit composé inhibant la couche visqueuse est réparti par enduction du dispositif avec un polymère contenant le composé inhibant la couche visqueuse.

35 20. Procédé selon la revendication 19, dans lequel ledit polymère a des propriétés de libération retardée.

21. Procédé selon la revendication 1, dans lequel ladite quantité efficace de composé inhibant la couche visqueuse, sur ou au voisinage de la surface du dispositif, est comprise entre environ 1 et environ 20 mM.

40 22. Procédé selon la revendication 1, dans lequel ledit composé inhibant la couche visqueuse est réparti sur ledit dispositif par une méthode comprenant:

45 l'exposition dudit dispositif médical, avant l'insertion ou l'implantation, dans une solution, ladite solution ayant une concentration comprise entre environ 1 mM et environ 1 M du composé inhibant la couche visqueuse; l'enlèvement dudit dispositif médical de ladite solution; le séchage dudit dispositif médical; et ledit dispositif médical étant inséré ou implanté dans un mammifère.

50 23. Procédé selon la revendication 1, dans lequel la quantité efficace dudit composé est répartie sur ledit dispositif médical par un procédé comprenant:

55 l'enduction dudit dispositif médical, avant l'insertion ou l'implantation, avec un polymère, ledit polymère ayant une concentration comprise entre environ 1 mM et environ 1 M d'un composé inhibant la couche visqueuse, pour inhiber ainsi la croissance de micro-organismes sur ledit dispositif médical lors de l'implantation ou de l'insertion dudit dispositif médical, et ledit dispositif médical étant implanté ou inséré dans un mammifère.

24. Procédé selon la revendication 23, dans lequel ledit polymère a des propriétés de libération retardée.

25. Procédé selon la revendication 24, dans lequel ledit dispositif est fait d'un polymère choisi dans le groupe constitué

par un matériau "silastique" ou autre matériau à base de silicone, le poly(téréphthalate d'éthylène) (PET), la polyglacine, la polydioxannone, le catgut chromé, le Nylon, la soie, le Dacron, le Dacron tricoté, le Dacron velours, une greffe artérielle bovine, le polyéthylène (PE), le poly(chlorure de vinyle) (PVC), un élastomère "silastique", un caoutchouc silicone, le PMMA [poly(méthacrylate de méthyle)], le latex, le polypropylène (PP), le titane, la cellulose, le poly(alcool vinylique) (PVA), le poly(méthacrylate d'hydroxyéthyle) (PHEMA), le poly(acide glycolique), le polyacrylonitrile (PAN), un copolymère fluoroéthylène/hexafluoropropylène (FEP), le Téflon (PTFE), des alliages Co-Cr, le PVC, un polyuréthane, un polyester, le polytétrafluoroéthylène et des polymères biologiques tels que le collagène.

- 5 10 26. Procédé selon la revendication 1, dans lequel la quantité efficace dudit composé est répartie sur ledit dispositif médical par une méthode comprenant l'exposition dudit dispositif, avant l'insertion ou l'implantation, avec ledit composé inhibant la couche visqueuse, ladite exposition étant suffisante pour enduire le dispositif avec une quantité de composé inhibiteur capable de réduire la quantité de croissance microbienne sur ledit dispositif, mais étant insuffisante pour avoir des effets favorables thérapeutiques systémiques.
- 15 27. Procédé selon la revendication 26, dans lequel ledit dispositif est un cathéter.
- 20 28. Procédé selon la revendication 1, dans lequel la quantité efficace dudit composé inhibant la couche visqueuse est une quantité, efficace pour réduire une thrombophlébite, d'un AINS.
- 25 29. Procédé selon la revendication 28, dans lequel ledit AINS est choisi dans le groupe constitué par l'acide salicylique, l'acide acétylsalicylique (Aspirine), le bisalicylate, l'acide benzylbenzoïque, le diflunisal, le fendosal, l'indométhacine, l'acémétacine, la cimétacine, le sulindac, la tolémétine, le zomépirac, le diclofénac, le fenclofénac, l'isoxépac, l'ibuprofène, le flurbiprofène, le naproxène, le kétoprofène, le fénoprofène, le bénoxaprofène, l'indoprofène, le pirprofène, le carprofène, l'acide méfénamique, l'acide flufenamic, le méclofénamate, l'acide niflumique, l'acide tolfénamique, la flunixine, la clonixine, la phénylbutazone, la féprazole, l'apazole, la triméthazone, la mofébutazone, la kébuzone, la suxibzone, le piroxicam, l'isoxicam et le ténoxicam.
- 30 30. Dispositif médical pouvant être inséré ou implanté, ayant un risque réduit de provoquer une infection après l'insertion ou l'implantation, comprenant un dispositif sur lequel est répartie une quantité, efficace pour l'inhibition de la couche visqueuse, d'un composé inhibant la couche visqueuse, ladite quantité efficace étant insuffisante pour avoir des effets favorables thérapeutiques systémiques.
- 35 31. Dispositif selon la revendication 30, dans lequel ledit composé inhibant la couche visqueuse est présent en une proportion comprise entre environ 1 et environ 20 mM.
- 40 32. Dispositif selon la revendication 30, caractérisé en ce que ledit dispositif comprend un polymère choisi dans le groupe constitué par un matériau "silastique" ou autre matériau à base de silicone, le poly(téréphthalate d'éthylène) (PET), la polyglacine, la polydioxannone, le catgut chromé, le Nylon, la soie, le Dacron, le Dacron tricoté, le Dacron velours, une greffe artérielle bovine, le polyéthylène (PE), le poly(chlorure de vinyle) (PVC), un élastomère "silastique", un caoutchouc silicone, le PMMA [poly(méthacrylate de méthyle)], le latex, le polypropylène (PP), le titane, la cellulose, le poly(alcool vinylique) (PVA), le poly(méthacrylate d'hydroxyéthyle) (PHEMA), le poly(acide glycolique), le polyacrylonitrile (PAN), un copolymère fluoroéthylène/hexafluoropropylène (FEP), le Téflon (PTFE), des alliages Co-Cr, le PVC, un polyuréthane, un polyester, le polytétrafluoroéthylène et des polymères biologiques tels que le collagène.
- 45 33. Dispositif selon la revendication 30, dans lequel ledit composé inhibant la couche visqueuse est un agent chélateur.
- 50 34. Dispositif selon la revendication 30, dans lequel ledit composé inhibant la couche visqueuse est un anti-inflammatoire non stéroïdien (AINS).
- 55 35. Dispositif selon la revendication 34, dans lequel ledit AINS est choisi dans le groupe constitué par l'acide salicylique, l'acide acétylsalicylique (Aspirine), le bis-salicylate, l'acide benzylbenzoïque, le diflunisal, le fendosal, l'indométhacine, l'acémétacine, la cimétacine, le sulindac, la tolémétine, le zomépirac, le diclofénac, le fenclofénac, l'isoxépac, l'ibuprofène, le flurbiprofène, le naproxène, le kétoprofène, le fénoprofène, le bénoxaprofène, l'indoprofène, le pirprofène, le carprofène, l'acide méfénamique, l'acide flufenamic, le méclofénamate, l'acide niflumique, l'acide tolfénamique, la flunixine, la clonixine, la phénylbutazone, la féprazole, l'apazole, la triméthazone, la mofébutazone, la kébuzone, la suxibzone, le piroxicam, l'isoxicam et le ténoxicam.

36. Dispositif selon la revendication 35, dans lequel ledit AINS est l'acide salicylique ou un sel de celui-ci.

37. Dispositif selon la revendication 35, dans lequel ledit AINS est l'ibuprofène.

5 38. Dispositif médical pouvant être inséré ou implanté selon la revendication 30, dans lequel la quantité efficace dudit composé inhibant la couche visqueuse est une quantité, efficace pour réduire une thrombophlébite, d'un AINS.

39. Dispositif selon la revendication 38, dans lequel ledit AINS est présent en une proportion comprise entre environ 1 et environ 20 mM.

10 40. Dispositif selon la revendication 38, dans lequel ledit AINS est choisi dans le groupe constitué par l'acide salicylique, l'acide acétsalicylique (Aspirine), le bis-salicylate, l'acide benzylbenzoïque, le diflunisal, le fendosal, l'indométhacine, l'acémétacine, la cimétacine, le sulindac, la tolémétine, le zomépirac, le diclofénac, le fenclofénac, l'isoxépac, l'ibuprofène, le flurbiprofène, le naproxène, le kétoprofène, le fénoprofène, le bénoprofène, l'indoprofène, le pirprofène, le carprofène, l'acide méfénamique, l'acide flufenamique, le méclofénamate, l'acide niflumique, l'acide tolfénamique, la flunixine, la clonixine, la phénylbutazone, la féprazole, l'apazole, la triméthazole, la mofébutazone, la kébuzone, la suxibuzone, le piroxicam, l'isoxicam et le ténoxicam.

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